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This Month in *AJP*

Defects in DNA Repair as a Causative Factor in the Pathogenesis of Medulloblastoma

Cerebellar medullobastoma is the most common of the highly malignant embryonal neoplasms of the central nervous system known as primitive neuroectodermal tumors (PNETs). A small fraction of these tumors appear in patients with hereditary cancer syndromes such as Li-Fraumeni syndrome (p53 mutations), Gorlin syndrome (mutations in *Patched*, *Ptc1* gene), and Turcot syndrome (mutations in *adenomatous polyposis colon*, *APC* gene). Nevertheless, single gene abnormalities do not explain the pathogenesis of medulloblastomas suggesting that other defects or combinations of defects are required to produce the tumor. Tong et al **(Am J Pathol 2003, 162:343–352)** hypothesized that DNA repair defects may play a key role in medulloblastoma formation. Poly (ADP-ribose) polymerase known as PARP-1 is activated by DNA breakage and its deficiency increases the incidence of some types of tumors. Tong et al produced PARP-1/p53 double knockout mice and report that these animals develop medulloblastomas (49% frequency) starting at 8 weeks of age. Tumor development is similar to that observed in humans and includes activation of the transcription factor Math1, alteration in the Ptc1/sonic hedgehog pathway, and chromosomal abnormalities. The work demonstrates that loss of function of components of the DNA repair machinery is directly associated with the development of medulloblastomas.

Anti-Vascular Therapy for Tumors Is Dependent on the Maturation of Tumor Blood Vessels

Anti-angiogenic therapy to control tumor growth has generated intense interest and is the subject of a large number of experimental studies and clinical trials. Despite the development of several promising agents, it is still unclear whether these agents would be effective in different kind of tumors or at various growth stages of specific tumors. Gee et al **(Am J Pathol 2003, 162:183–193)** hypothesized that response to anti-angiogenic therapy may vary depending on the maturation of tumor blood vessels. They studied blood vessels in transplanted mouse tumors and the effects of the anti-angiogenic agent interleukin-12 (IL-12). Tumor vessels could be grouped into three categories depending on their stage of maturation, based on their size, rate of endothelial cell proliferation, and pericyte covering. Treatment with IL-12 produced tumor ischemia and cell death. However, response to antivascular therapy was strongly dependent on the maturation stage of the microvasculature. IL-12 reduced angiogenesis and caused endothelial cell apoptosis in vessels that did not contain pericytes, leading to selective loss of vessels with a low degree of maturation. As the fraction of mature, pericyte-covered vessels increased after IL-12 therapy, it may be expected that the tumors would become more resistant to anti-angiogenic agents. The work demonstrates that angiogenic therapy is more effective for tumors that contain immature vessels not enveloped by pericytes and that selective elimination of these vessels may lead to resistance to therapy.

Insulin-Degrading Enzyme Is Reduced in Alzheimer's Disease Patients with APOE + ϵ4 Genotype

β-amyloid protein (Aβ) in senile plaques of Alzheimer's disease (AD) is generated by cleavage of the β-amyloid precursor protein (APP). Catabolism of APP occurs normally and Aβ levels may be regulated by increased production or decreased clearance of the protein. The enzyme known as insulin-degrading enzyme (IDE) is involved in the degradation and clearance of Aβ in the brain and is capable of degrading APP cleavage products. IDE is a metallo-protease that also acts on other peptides including insulin, amylin, and atrial natriuretic hormone, with preferential affinity for insulin. Cook et al **(Am J Pathol 2003, 162:313–319)** measured IDE expression in hippocampal tissue of AD patients and normal subjects. IDE activity as well as IDE mRNA was reduced by approximately 50% in AD patients with apoprotein E (APOE) + ϵ4 genotype compared to normal individuals and APOE − ϵ4 AD patients. These results suggest that IDE deficiency may play a role in enhancing Aβ deposition in ϵ4-positive AD patients probably by decreasing Aβ degradation.

Inactivation of Mannose 6-Phosphate/IGF2 Receptor in Liver and Muscle

The mannose 6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2R) is a multifunctional receptor that interacts with intra-and extracellular ligands that include the latent complex of TGFβ and insulin-like growth factor 2. By controlling the cellular availability of these and other factors, the receptor is thought to play an important role in apoptosis and cell proliferation. In addition, loss of function of the *M6P/IGF2R* gene has been found in several human cancers, indicating that it may function as a tumor suppressor gene. M6P/IGF2R knockout mice die around the time of birth with an

overgrowth phenotype and defects in skeletal and cardiac muscle, as well as the lungs. To overcome this problem and permit the study of M6P/IGF2R functions in adult animals, Wylie et al (Am J Pathol 2003, 162:321–328) generated mice containing a *M6P/IGF2R* gene in which exon 10 is flanked by lox P sites. Exposure of this site to Cre-recombinase driven by either albumin or muscle creatine kinase promoters resulted in deficiency of the receptor in liver and skeletal and cardiac muscle. These animals appear to develop normally and are viable. The establishment of mouse models of tissue-specific inactivation of M6P/IGF2R will permit the analysis of the role of the receptor in various cellular processes including proliferation, apoptosis, and trafficking of lysosomal enzymes.

Liver Stem-Like Cell (Oval Cell) Proliferation Occurs Only in Areas of Defective Hepatocyte Replication

Hepatocytes which are normally quiescent rapidly replicate after partial hepatectomy or acute carbon tetrachloride-induced injury. If hepatocytes cannot respond to a growth stimulus and replicate, stem-like cells, called oval cells, proliferate. Thus, it is thought that oval cells constitute a reserve compartment in the liver that is activated only if hepatocytes fail to proliferate. Several experimental protocols have been used to examine the relationships between hepatocyte and oval cell proliferation. However, most of these observations were not done in a single liver that contains separate areas of normal hepatocyte replication and oval cell proliferation associated with hepatocyte damage. Braun et al (Am J Pathol 2003, 162:195–202) used transgenic mice that overexpress urokinase-type plasminogen activator (μPA) to examine whether oval cell proliferation in the liver of these animals would be confined to areas of injury. These mice develop liver disease as a consequence of μPA expression but in many areas of the liver, hepatocytes lose the μPA transgene. After partial hepatectomy, hepatocytes without the transgene replicate and maintain normal tissue structure without activation of the oval cell compartment. In contrast, extensive oval cell proliferation occurred in areas containing damaged hepatocytes expressing μPA. In areas of injury, oval cells were closely associated with stellate cells and laminin deposition. The work demonstrates a clear demarcation between areas of hepatocyte and oval cell proliferation in a single liver. The precursor cells were present only in areas of injury in which hepatocytes did not maintain a proliferative response after partial hepatectomy.

Histological, Phenotypic, and Molecular Analysis of Primary Mediastinal B-Cell Lymphomas

Primary mediastinal (thymic) B-cell lymphoma (PMBL) is a relatively recently recognized entity among tumors of hemopoietic and lymphoid tissue. A considerable number of studies have been performed to characterize the genetic abnormalities in these tumors but results remain controversial. The International Extranodal Lymphoma Study Group (IELSG) analyzed the morphological, phenotypic, and molecular alterations in 137 PMPLs. The report from these studies is presented by Pileri et al (Am J Pathol 2003, 162:243–253). Among the novel findings is the detection of mutations in the *BCL-6* gene in more than half of the cases. Immunoglobulin production by these tumors was not detectable by immunohistochemistry or *in situ* hybridization but expression of the transcription factors OCT-2, BOB-1, and PU-1 was not altered. The study also supports the notion that PMBLs originate from germinal or post-germinal center cells.